Ain Shams University
Faculty of Women for Arts,
Science and Education.
Chemistry Department

Synthesis of Heterocyclic Compounds via Enaminone

A Thesis Submitted for the degree of M.Sc. in Science
(Organic Chemistry)

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ABSTRACT

The enaminones 2-oxo-4-(phenylamino)pent-3-ene **1**, 4-[2-(1-methyl-3-oxo-but-1-enylamino) ethylamino]-pent-3-en-2-one **2** and 5,5-dimethyl-3-(phenylamino)cyclohex-2-enone **3** were prepared under solvent free condition using ceric ammonium nitrate (CAN) as catalyst.

The reactivates of **1**, **2** and **3** towards different reagents were studied and heterocycles and polyfunctionally heterocyclic compounds were obtained

The newly synthesized compounds was elucidated by elemental analysis and spectral data (IR,^{1}HNMR,MS).

The selected tested compounds showed a bacterial activity while all of them did not show any activity toward fungi.

Acknowledgment

The author would like to express her full respectful thanks to Dr.Nadia Iskandar Abdel Sayed ,Assistant professor of Organic Chemistry ,Faculty of Women for Arts, Science and Education ,Ain Shams University for suggesting the title of the thesis, guiding through all stages of the work , teaching theoretical and practical skills in organic chemistry and being a great help and support from the beginning to the end of the work.

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Last and certainly not least I would like to thank my family .They have encouraged me through my life, made a great impact on my personality ,thanks for teaching me how to exist.

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Safaa Ebrahem

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ملخص البحث باللــغة العربية

الإنــامينونات**1 و 2 و 3** تم تحضيرهم بإستعمال العامل الحفاز سيرك أمونيم نيترات وبدون وجود اى مذيب في وسط التفاعل.

فبتفاعل مركب 2-أوكسو-4-فينيل امينوبنتا -3-إين **1** مع المالونونيتريل في وجود الداى ميثيل فورماميد القاعدي أعطى مشتق 2و4-داينامين **7** الذى بتفاعله مع أنهيدريد الخليك فى وجود حامض الهيدزوكلوريك أعطي مشتق 1و2-داى هيدروبيريدين **8**.

أيضا تفاعل مركب **1** مع ايثيل سيانو اسيتات فى البيريدين وأعطى مشتق البيران **11**. و بتفاعل مركب **1** مع1و2و4 -تريازول امين فى الايثانول أعطى مشتق تريازوليل بنتينون**12** الذى تحولق وأعطى مشتق تريازوليل بيريميدين الملتحم الحلقة**13**.

وبتفاعل **1** مع الهيدرازين هيدرات الاحادى أعطى مشتق البيرازول الملتحم الحلقه **15**

وبتفاعل **1** مع حامض الهيبيوريك فى وجود انهيدريد الخليك أعطى مشتق البيرانون **18.**

وبتفاعل الانامينون 4-(2-(1-ميثيل-3-اوكسو- بيوت-1-اينيل امينو)-1إيثيل امينو-بنت-2-اين-2-اون **2** .مع المركبات التى تحتوى على مجموعة الميثلين النشطة سواء باستخدام كميات متساوية أو باستخدام 1 : 2 مول (ايناميون: كاشف المثيلين النشط)أعطى ناتج واحد فقط بنسبة (إنامينون:كاشف الميثيلين النشط).

وبتفاعل **2** مع المالونو نيتريل أعطى مشتق الداينامين **21** الذى بدوره يتحولق بغلية مع انهيدريد الخليك فى وجود حامض الهيدروكلوريك الى مشتق الداى هيدروبيريدنون **22**.

وبنفس الطريقة تفاعل **2** مع السيانو اسيتاميد اومع سيانواسيتانيليد أومع الايثيل أسيتو أسيتات أومع الايثيل سيانواسيتات أعطى المركبات **21و22&26و22& 29و30&33و22** على الترتيب.

وبتفاعل مركب **2** مع الهيدروكسيل امين هيدروكلوريد أعطى ناتجين مشتق البيرازوليل إيثيل أمين بنتينون **34** ومشتق البيرازوليل إيثيل بيرازول **35**.

وبتفاعل مركب الإنامينون 5،5-داى ميثيل -3-(فينيل أمينو) سيكلوهكسا-2-إينون **3** مع كل من الديازونيم هيتيروسيكليك أمين (3-أمينو1و2و4-تريازول ،5-أمينو –تيترازول و 2-أمينو بنزإيميدازول) يعطى المركبات **37و 40 و42و45و47** على الترتيب .

تفاعل الانامينون **3** مع المالونونيتريل عن طريق 1و4-الاضافه لميكل الى أعطي مشتق مالونونيتريل سيكلو هكسانون **49** وبتفاعل الأخير مع اليوريا أعطى مشتق إيمينوبيريمدينون سيكلو هكسانون**53**.

وقد تم إثبات التراكيب البنائية لجميع المركبات الناتجه إستنادا علي كل من التحاليل الكمية الدقيقة والتحاليل الطيفية.

وقد تم دراسةالتأثير البيولوجي لبعض المركبات المختارة ضد أنواع من البكتيريا سالبة الجرام والبكتيريا موجبة الجرام والفطريات وقد وجد ان هذه المركبات أظهرت نشاط بكتيرى بينما ليس لها نشاط تجاه الفطريات وعلى ذلك نستطيع ان نستخلص ان المركبات الجديدة المحضرة لها اهمية بيولوجيه مقارنة بالدليل تيترا سيكلين.

I-Recent Development in the Chemistry of Enaminones

1-Introduction

Enaminones, being bioactive compounds, are used as a key intermediate in the synthesis of various heterocyclic compounds**,** naturally occuring alkaloids and polydentate reagents it has also been found that this kind of moiety is useful for the synthesis of those compounds that possess antiepileptic, molluscicidal and larvicidal activities ***(Kidwai, M. et al., 2009; Abass, M. and Mostafa, B.B.2005 ;El-Shennawy, A.M.2007 et al., and Martinez, J.C.G. et al., 2006*)**.

Enaminones derivatives have attracted a great deal of interest due to their biological activities such as anti HIV***(Mamos, D. et al.,1990,C.A. 1989)***, anti-tumor ***(Kobayashi, G. et al.,C.A. 1978),*** anti-hypertensive **(*Ferrarine, P.L. et al., 1999)***, anti-allergic ***(Soliman, F.S. et al., 1977*)**,** anti-inflammatory ***(Ram,V.J. et al., 1999)***, anti-bacterial **(*Fujisawa, W. 1988; C.A. 1989)*** and anti-shock activities ***(Drown, R.E.et al., 1964).***

The term enaminones is related to compounds that contain the conjugate system N**-C=C-C=O*(Ivanov, I. et al., 2007 and Mahmud, T. et al., 2009).***

Enaminones have two electron-deficient centres at C-1 and C-3, while the C-2 and amino functions are electron rich .They can thus react with both electrophiles and nucleophiles **(Figure 1*)(Stanovnik, B.and Svete,J. 2004 and Sheibani, H. et al., 2006)***.

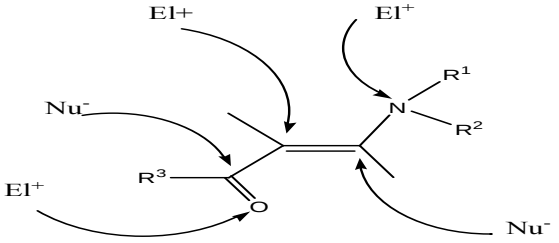


Figure 1

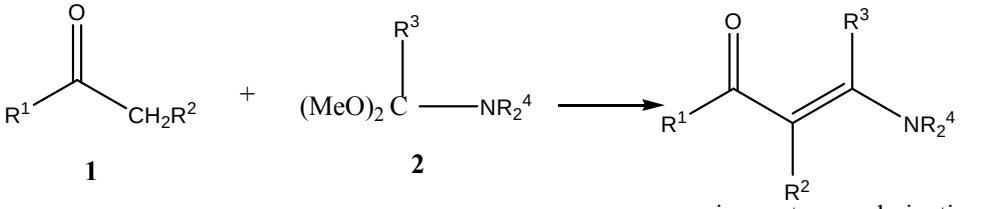
Enaminones are very stable compounds and can be easily prepared, starting from cheap and easily available starting materials.

2-Synthetic approaches to enaminones

2.1. Condensation reactions

2.1.0 Condensation of active methyl and methylene ketones with dimethylformamide dimethyleacetal

Active methylene ketones **1** condensed readily with dialkylamino dimethyl acetals **2** to yield the enaminones **3.**



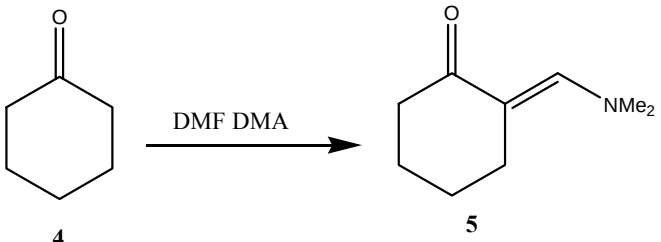
1 **2**

aminopentenone derivatives

3

In general, enaminone formation had been conducted in refluxing aromatic hydrocarbons***, (Lue, P.and Greenhill, J.V.,1997;Al-Omran, F.et al., 1998; Caubere, C.et al., 1994;Reis, L.V.et al.,1994;Selic, L.et al.,.1997and Svete, J. et al .,1997*)**,** ethanol, ***(Zupancic, S. et al., 2001)*** ether***, (Hegde, S.G.and Jone,C.R., 1993*)**, under nitrogen***, (San Martin, R.et al., 1994)*** toluene***, (Reis, L.V. et al., 1994)***, DMF***(Sorsak, G.et al., 1998)*** or without solvent ***(Reidlinger, C. et al.,1998 and Al-Omran, F. et al.,2001*)**.** Both cyclic and acyclic ketones condense readily under these conditions.

The condensation of cyclohexanone **4** with N, N-dimethylformamide dimethyl acetal, for example, (DMF DMA) afforded the enaminone **5** in 47 % yield ***(Schuda, P.F. et al.,1986)***.



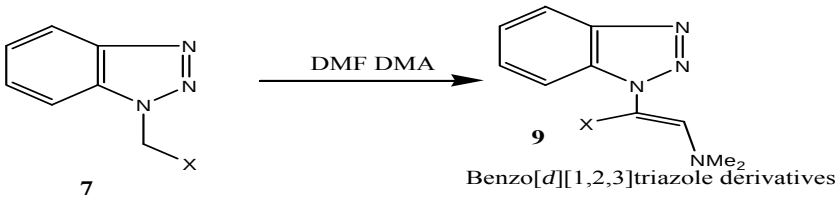
4 **5**

(*E*)-2-((dimethylamino)methylene)cyclohexanone

Recently, the enaminones **8** and **9a–c** could be obtained in 73 and 82% yield, respectively, via the condensation of **6** and **7a–c** with DMF DMA in xylene ***(Al-Omran, F. et al.,1998 and Al-Omran, F. 2000).***

6 8

N-((*E*)-1-(dimethylamino)-3-oxobut-1-en-2-yl)acetamide

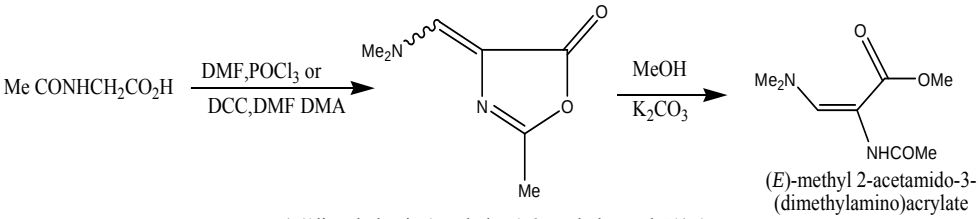


7 9

Benzo[*d*][1,2,3]triazole derivatives

a)X=COMe b)x=COPh c) X=CN

N-Acetylglycine upon reflux with dimethylformamide in the presence of phosphorus trichloride or treatment with N,N-dicyclohexyldicarbodiimide (DCC) and DMF DMA afforded the cyclic enaminone **10**, which on methanolysis in the presence of potassium carbonate afforded the enamino ester **11** in 78% yield ***(Kralj,L. et al ., 1997)***.



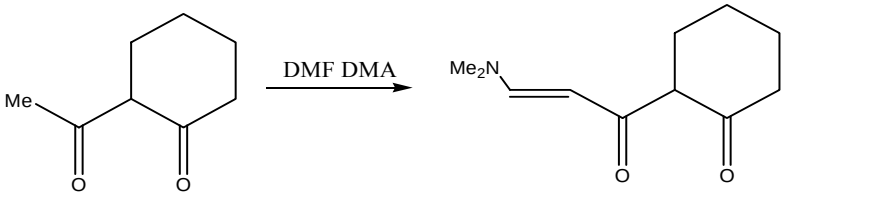
4-((dimethylamino)methylene)-2-methyloxazol-5(4*H*)-one

10

(*E*)-methyl 2-acetamido-3-(dimethylamino)acrylate

11

Treatment of 2- acetylcyclohexanone **12** with (DMF DMA) in refluxing xylene yielded enaminone **13** in 67% yield ***(Al-Omran,F. et al., 2001).***

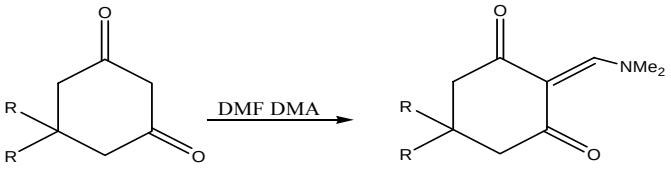


12

2-((*E*)-3-(dimethylamino)acryloyl)cyclohexanone

13

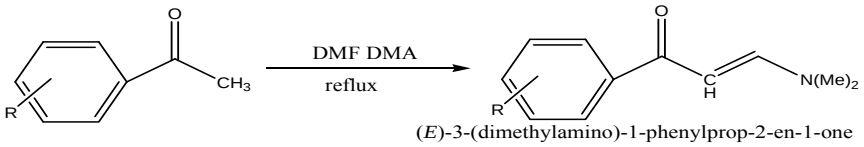
The enaminones **15a,b** were synthesized in 60-70% yield via condensation of **14a,b** with DMF DMA in refluxing xylene***(Al-Saleh,B. et al., 2002).***



14 2-((dimethylamino)methylene)cyclohexane-1,3-dione derivatives

14,15 a) R=Ph **15**
b) R=Me

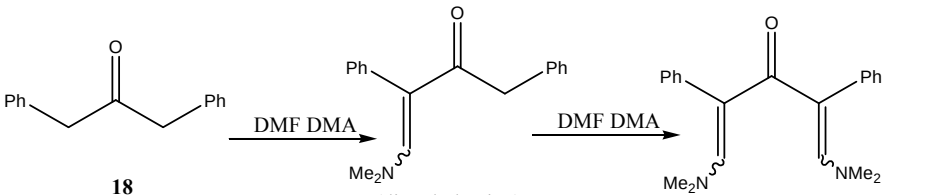
The condensation of compound **16a-f** with DMF DMA yielded the enaminone **17a-f** ***(El-Taweel, .M.A.A.and Elnagdi, M.H. 2001and Zhang, S.Q. et al., 2002).***



(*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one

16a)R=H b)R=P-Cl c)R=p-CH_3 **17a-f**
d)R=p-OCH_3 e)R=p-F f)R=2,4-dCl

Reacting 1, 3-diphenyl-propan-2-one **18** with equimolecular amount of DMF DMA afforded the enaminones **19** in absence of solvent, this when reacted with another equimolecular amount of DMF DMA afforded the dienaminone **20*(Hook,J. M. and Mander, L.N. 1980; Almazroa , S. et al., 2004 and Abdel-Khalik, M.M.et al., 2004).***



18

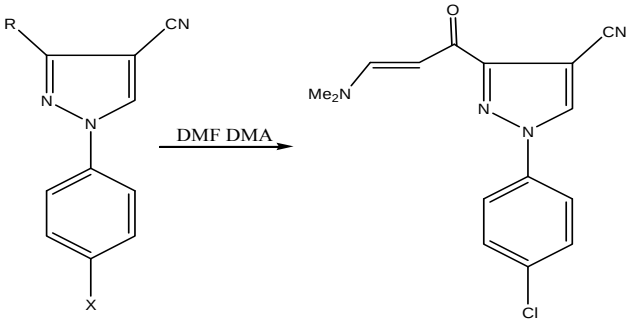
4-(dimethylamino)-1,3-diphenylbut-3-en-2-one

19

1,5-bis(dimethylamino)-2,4-diphenylpenta-1,4-dien-3-one

20

Compound **21** condensed with DMF DMA to afford the enaminone **22** in 75% yield (***Ghozlan,S.A.S. et al., 2005).***

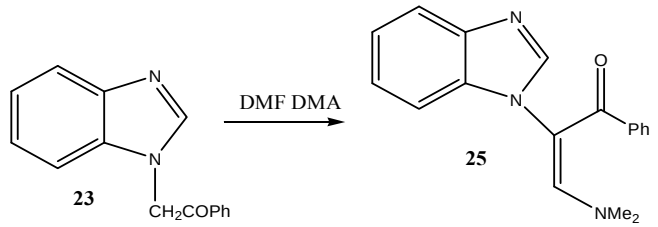


21 X=Cl
R=$COCH_3$

1-(4-chlorophenyl)-3-((*E*)-3-(dimethylamino)acryloyl)
-1*H*-pyrazole-4-carbonitrile

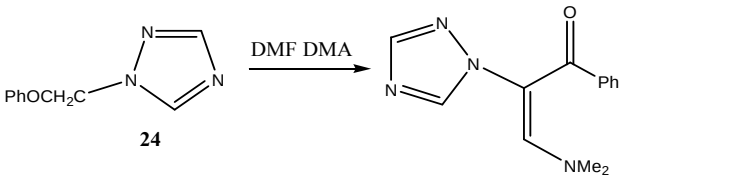
22

Both compounds **23 and 24** condensed readily with DMF DMA in xylene to afford the enaminones **25, 26*(Abdel-Megid, M. et al., 2002)***



23 **25**

(*E*)-2-(1*H*-benzo[*d*]imidazol-1-yl)-3-
(dimethylamino)-1-phenylprop-2-en-1-one

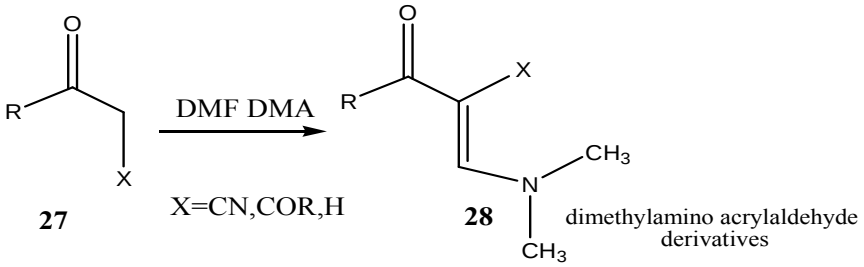


24

(*E*)-3-(dimethylamino)-1-phenyl-2-
(1*H*-1,2,4-triazol-1-yl)prop-2-en-1-one

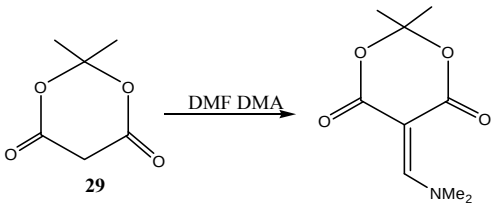
26

The reaction of active methylene ketones of general formula **27**(where x is electron withdrawing group or hydrogen) readily condensed with DMF DMA to yield enaminones **28*(Al-Zaydi,K.M. et al., 2000 and Toche, .B. et al., 1998)***.



27 **28**

Meldrum acid **29** condensed with DMF DMA to yield the enaminone **30**.Acetaldehyde **31** also condensed with DMF DMA to yield **32(*Blacke, A.J. et al., 1989;Hickson, C.L. et al., 1986 and Mcnab, H. and Monhan, L.C., 1988).***



29

5-((dimethylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione

30

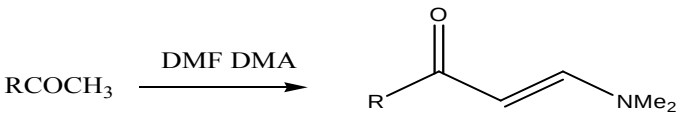
31

3-(dimethylamino)acrylaldehyde

32

Enaminones **34** could be obtained in 70-80% yield via refluxing a mixture of methyl ketones **33** with little excess of DMF DMA (1:1.2 moles) for six hours in absence of solvent. ***(Hassanien, A. A. et al., 2003).***

Attempted preparation of **34c, d** by refluxing the respective methyl ketone with DMF- DMA in refluxing acetic acid ***(Al-Mousawi, S.M. et al., 1999 and Almazroa,S. et al.,2004)*** or in toluene *solution* ***(Abdel-Khalik , M.M. et al., 2000).***



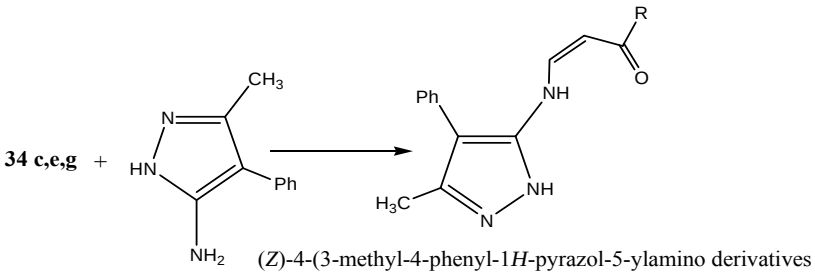
33 R=Me

34

(*E*)-4-(dimethylamino)propenone

a)R=Me
b)R=Ph
c)R=4-Cl-C_6H_4
d)R=2-$NO_2C_6H_4$
e)R=Thienyl
f)R=Furyl
g)R=4-$CH_3C_6H_4$

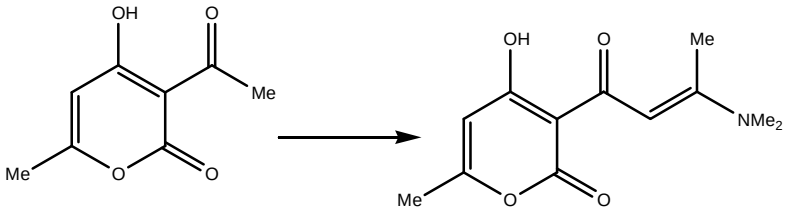
The enaminones **34c, e, g** reacted with the aminopyrazole derivative **35** to yield the enaminones **36c, e, g *(Almazroa , S. et al., 2004).***



(*Z*)-4-(3-methyl-4-phenyl-1*H*-pyrazol-5-ylamino derivatives

35 **36c,e,g**

The fungicidal dehydroacetic acid **37** condensed with N,N-dimethylacetamide dimethyl acetal yielded 72% of the enaminone **38*(Lowe, W. 1978 and Lowe, W. et al., 1994).***

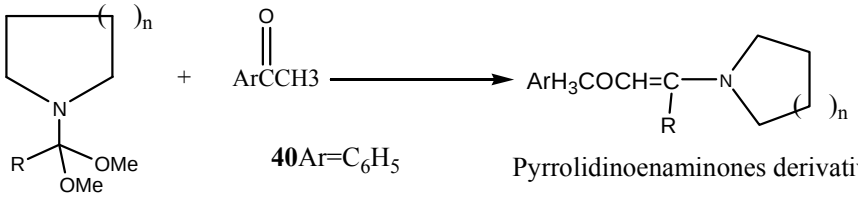


37

4-hydroxy -6-methyl-3-(3-dimethylamino)
-1-oxobut-3-enyl)2-pyranone

38

The cyclic amide acetals **39** condensed with aryl methyl ketones such as **40** yielding the Pyrrolidinoenaminones **41*(Ahuja, P. et al ., 1983 ; Dannhardt, V., G.et al., 1987, 1997 and Dannhardt, V.G. and Bauer, A., 1996).***



40Ar=C_6H_5

Pyrrolidinoenaminones derivatives

39

R=H,Me,Et;n=1,2

41

Azolylmethylketones **42-45** condensed with DMF DMA to yield enaminones **46-49.**This condensation has been achieved in a microwave oven within few minutes instead of several hours in refluxing xylene or in absence of solvent***(Al-Saleh, B.et al.,2004, 2003, 2002, 2001***